REMARKS

Applicants thank the Examiner for his review of the instant application. Applicants have amended the paragraph [0124] of the specification to include the following language:

> Capsules are solid dosage forms in which the drug substance is enclosed in either a hard or soft, soluble container or shell of a suitable form of gelatin. Although development work has been done on the preparation of capsules from methylcellulose and calcium alginate, gelatin, because of its unique properties, remains the primary composition material for the manufacture of capsules. The hard gelatin capsule, also referred to as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely surrounding the drug formulation. The soft elastic capsule (SEC) is a soft, globular, gelatin shell somewhat thicker than that of hard gelatin capsules.

This language is taken from Rudnic et al., Chapter 89 of *Remington's Pharmaceutical Sciences*, 18th Ed., pages 1658 and 1662, copies of which are attached hereto as Exhibit 1 for the Examiner's convenience. Applicants have added the above text, which was incorporated by reference in ¶[0176], to make explicit that Applicants contemplate customary capsules having a shell (typically made of gelatin) enclosing a single compartment containing the pharmaceutical formulation of active compound(s) and carriers and/or excipients. In addition, as ¶[0124] makes clear, Applicants also contemplate multicompartment hard capsules with control release properties and water permeable capsules with a multi-stage drug delivery system:

> ***Further***, multicompartment hard capsules with control release properties as described by Digenis et al., U.S. Pat. No. 5,672,359, and water permeable capsules with a multi-stage drug delivery system as described by Amidon et al., U.S. Pat. No. 5,674,530 may also be used to formulate the compositions of the present invention. *Specification* at ¶[0124] (emphasis added).

Applicants maintain that no new matter was added in the amendment of ¶[0124], as Applicants are permitted to add the actual text of material incorporated by reference:

> The information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed. Replacing the identified material incorporated by reference with the actual text is not new matter. *M.P.E.P. §2163.07(b)* (emphasis added).

Applicants have also amended paragraph [0174] of the specification to correct an obvious error. Figure 3 shows that most of the oligonucleotide is released quickly from granules comprising 25% bioadhesive, and that in contrast, less oligonucleotide is released from the

granules comprising 50% bioadhesive in the earlier fractions. This is consistent with the data in Figure 2, and ¶[0172], which states that "the largest amount of bioadhesive (50%) released the least amount of oligonucleotide at 3, 6, 10 and 15 minutes." Applicants submit that the correction of the obvious error in ¶[0174] does not constitute the addition of new matter. *See M.P.E.P. §2163.07 II* ("An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction.").

Applicants have amended claims 30 and 40 to delete the phrase " in a single compartment capsule" and to clarify the claims. Applicants have added new claims 43-55. Support for these claims can be found throughout the application as filed, for example, at ¶¶[0017], [0040], [0124], [0131]. Applicants submit that no new matter has been added. Claims 30-55 are presented for examination. For the reasons discussed below, Applicants respectfully traverse the rejections of the pending Office Action.

35 U.S.C. § 112, First Paragraph, Written Description and Enablement

The Examiner has rejected claims 30-42 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, asserting that the addition of the term "single compartment capsule" constitutes new matter. The Examiner asserts that while paragraph [0124] indicates that capsules "can be any of a genus of formulations that are well known in the art," only two species are specifically recited, "multicompartment hard capsules and water permeable capsules." *Office Action* at 4. The Examiner concludes that "[s]ince the disclosure of a broad genus does not anticipate every species which it encompasses, the disclosure of paragraph 0124 does provide proper support for a single compartment capsule." *Office Action* at 4. Presumably, given the instant rejection, the Examiner meant to state that paragraph 0124 does not provide proper support for a single compartment capsule. Applicants respectfully traverse.

Paragraph [0124] makes clear that Applicants contemplated the use of single compartment capsules. Applicants disclose the use of capsules, and state that "**[f]urther**, multicompartment hard capsules..." are also contemplated. As used in paragraph [0124], "further" clearly means in addition. If it is contemplated that "multicompartment hard capsules" can be used in addition to something else, the obvious question is: "In addition to what?" The

answer that would be obvious to anyone of skill in the art is that multicompartment capsules are contemplated in addition to single-compartment capsules. The Examiner must explain why one of skill in the art would not recognize this basic idea.

Applicants respectfully submit that the Examiner is confusing the test for anticipation, with the test for written description. It is true that a broad genus does not always anticipate a species, but this has nothing to do with adequate written description. All that is required to satisfy the written description requirement is that "the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed.'" *M.P.E.P. §2163*, citing *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563-4, 19 U.S.P.Q.2d at 1116. Applicants remind the Examiner that "[t]he examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 U.S.P.Q. at 97." *Id.* Only then does the Applicant need to respond to the Examiner's arguments. Applicants submit that the Examiner has not sufficiently explained why one of skill in the art would not recognize a single-compartment capsule in Applicants' disclosure.

The Examiner has relied on 37 C.F.R. § 1.118(a) to state that regardless of what was known in the art, no new matter can be added to the disclosure. However, if one of skill in the art would recognize at the time of filing that Applicants were in possession of single-compartment capsules as now claimed, the amendment of the claims does not constitute new matter. It is incumbent on the Examiner to explain how one of skill in the art would not have recognized that Applicants were in possession of the invention as now claimed.

In addition, Applicants note that the Examiner has stated that "McKay teaches that the therapeutic formulation can be comprised in a capsule or tablet, which as described by McKay would be a single compartment capsule." *Office Action* at 7. To anticipate, every claim element must be explicitly or inherently disclosed in the cited reference. As McKay does not explicitly disclose a "single compartment capsule," the Examiner must be asserting that McKay's general description of capsules is an inherent disclosure of a "single compartment capsule," or a small enough genus that one of skill in the art would immediately envision a "single compartment capsule."

Applicants agree, and note that it follows from the Examiner's rejection that Applicants' general disclosure of capsules must also be an inherent disclosure of single compartment capsules. Thus, the Examiner should withdraw the written description rejection since the inherent disclosure provides written description support for a "single compartment capsule." *See M.P.E.P. §2163.07(a)* (an application can be amended to include inherent matter without introducing prohibited new matter).

Applicants note that claims 30 and 40 have been amended such that they no longer recite "single compartment capsule," although the phrase is found in new claims 48 and 54. In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the pending claims over the recitation of the phrase "single compartment capsule."

The Examiner has also rejected the claims as lacking enablement, stating that "since a disclosure cannot teach one to make or use something that has not been described." *Office Action* at 5. For at least the above reasons, Applicants submit that the pending claims are adequately described, and therefore request that the Examiner withdraw the enablement rejection of the pending claims as well.

35 U.S.C. §§ 102(b) and 103(a) – Anticipation and Obviousness

The Examiner has rejected claims 30-36, 38-42 under 35 U.S.C. § 102(b) as anticipated by McKay, US Patent No. 5,877,309. The Examiner asserts that McKay teaches a method comprising administering to a subject a composition comprising all of the structural elements of the instant claims, and therefore, the method of McKay would necessarily have the same results as the instant claimed method. *Office Action* at 7. The Examiner also rejects pending claims 30, 33, and 37 under 35 U.S.C. § 103(a) as obvious over McKay in view of Bennett. Applicants respectfully traverse.

Applicants reject the Examiner's assertion that McKay teaches administration of a composition "comprising all of the structural elements of instant claims." *Office Action* at 7. The Examiner has previously stated that McKay does not anticipate or render obvious the pending claims. In the Office Action mailed September 7, 2005, the Examiner stated:

> Applicant's arguments, see page 4 of the communication filed 6/22/2005, with respect to the rejection(s) of claim(s) under 35 USC 102(b) and 35 USC 103(c)

have been fully considered and, in light of the amendment, are persuasive. Therefore, the rejection has been withdrawn. *Office Action mailed 9/7/05* at 6.

The rejections referred to are the rejection of the pending claims under 35 U.S.C. §§ 102(b) and 103(a) over McKay. The arguments on page 4 of the communication filed 6/22/2005 which the Examiner previously found persuasive are as follows:

> Claims 28-36, 38 and 39 are rejected under 102(b) as being anticipated by McKay (USP 5,877 ,309). The Applicants submit that the current claim is not anticipated by McKay who teaches only monolithic formulations in which the various components are mixed homogeneously. Claim 30 teaches a method using two populations of carrier particles which is clearly distinct from the teachings of McKay; therefore, the rejection of the claim 30 under 35 USC 102 (b) is traversed. As the remaining pending claims in the rejection are dependent, either directly or indirectly on claim 30, they are also not anticipated by McKay. Therefore, the rejection of claims 30-36, 38 and 39 under 35 USC 102(b) is traversed.
>
> Claims 30, 33 and 31 are rejected under 35 USC 103(a) for obviousness over McKay in view of Bennett (USP 5,514,788). The Applicants submit that McKay does not make obvious the use of two populations of carrier particles as claimed in the instant invention, and that this deficiency is not overcome by the teachings of Bennett. Therefore, claim 30 is not obvious over McKay in view of Bennett. As claims 33 and 37 are dependent on the nonobvious claim 30, they are also not obvious in view of the references. Therefore, the rejection of claims 30, 33 and 37 under 3S USC 103(a) is traversed. *Submission filed 6/22/2005* at 4.

Applicants reassert these arguments. As such, McKay does not disclose the use of two populations of carrier particles as claimed in the instant application, and therefore does not anticipate or render the pending claims obvious. Therefore, Applicants request that the Examiner again withdraw the rejection of the pending claims as anticipated or obvious over McKay, alone or in combination with Bennett.

In addition, Applicants note that in the Office Action mailed September 7, 2005, the Examiner stated that the Teng et al. reference disclosing compositions comprising enhancers and carriers or excipients including HPMC, "does not explicitly teach that the drug (i.e., the oligonucleotide) is comprised in a first population of carrier particles with a bioadhesive and that the penetration enhancer is comprised in a second population of carrier particles...." *Office Action mailed 9/7/05* at 4. This interpretation of the Teng reference also applies to the McKay reference. Accordingly, McKay's description of enhancers and carriers or excipients would similarly not teach that the drug is comprised in a first population of carrier particles with a

bioadhesive and that the penetration enhancer is comprised in a second population of carrier particles.

Finally, Applicants note that the pending claims recite administration of compounds having particular structural features. Even if the administration of the composition of McKay would necessarily have the same results as the instant claimed method as asserted by the Examiner, a point which Applicants do not concede, McKay does not anticipate or render obvious the pending claims because McKay does not teach or suggest all of the structural elements of the pending claims, e.g. a first population of carrier particles comprising a drug-bioadhesive component; and a second population of carrier particles comprising a penetration enhancer.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the pending claims under 35 U.S.C. §§ 102(b) and 103(a) as anticipated and obvious over McKay, alone or in combination with Bennett.

Objections to Claim Form

Claims 41 and 42 are objected to under 37 C.F.R. § 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. *Office Action* at 9.

In view of the amendment of claims 30 and 40, Applicants submit that claims 41 and 42 are now in proper dependent form as they further limit the subject matter of claims 30 and 40, respectively. Applicants therefore request that the Examiner withdraw the objection to claims 41 and 42.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: May 25, 2007

By: _____

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052207

EXHIBIT 1

CHAPTER 89

Oral Solid Dosage Forms

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Drug substances most frequently are administered orally by means of solid dosage forms such as tablets and capsules. Large-scale production methods used for their preparation, as described later in the chapter, require the presence of other materials in addition to the active ingredients. Additives also may be included in the formulations to enhance the physical appearance, improve stability and aid in disintegration after administration. These supposedly inert ingredients, as well as the production methods employed, have been shown in some cases to influence the release of the drug substances.[1] Therefore care must be taken in the selection and evaluation of additives and preparation methods to ensure that the physiological availability and therapeutic efficacy of the active ingredient will not be diminished.

In a limited number of cases it has been shown that the drug substance's solubility and other physical characteristics have influenced its physiological availability from a solid dosage form. These characteristics include its particle size, whether it is amorphous or crystalline, whether it is solvated or nonsolvated and its polymorphic form. After clinically effective formulations are obtained, variations among dosage units of a given batch, as well as batch-to-batch differences, are reduced to a minimum through proper in-process controls and good manufacturing practices. The recognition of the importance of validation both for equipment and processes has greatly enhanced assurance in the reproducibility of formulations. It is in these areas that significant progress has been made with the realization that large-scale production of a satisfactory tablet or capsule depends not only on the availability of a clinically effective formulation but also on the raw materials, facilities, personnel, validated processes and equipment, packaging and the controls used during and after preparation (Fig 89-1).

Fig 89-1. Tablet press operators checking batch record in conformance with Current Good Manufacturing Practices (courtesy, Lilly).

Tablets

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or molding methods. They have been in widespread use since the latter part of the 19th century and their popularity continues. The term *compressed tablet* is believed to have been used first by John Wyeth and Brother of Philadelphia. During this same period, molded tablets were introduced to be used as "hypodermic" tablets for the extemporaneous preparation of solutions for injection. Tablets remain popular as a dosage form because of the advantages afforded both to the manufacturer (eg, simplicity and economy of preparation, stability and convenience in packaging, shipping and dispensing) and the patient (eg, accuracy of dosage, compactness, portability, blandness of taste and ease of administration).

Although the basic mechanical approach for their manufacture has remained the same, tablet technology has undergone great improvement. Efforts are being made continually to understand more clearly the physical characteristics of tablet compression and the factors affecting the availability of the drug substance from the dosage form after oral administration. Compression equipment continues to improve both as to production speed and the uniformity of tablets compressed. Recent advances in tablet technology have been reviewed.[8-13]

Although tablets frequently are more discoid in shape, they also may be round, oval, oblong, cylindrical or triangular. They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration. They are divided into two general classes, whether they are made by compression or molding. Compressed tablets usually are prepared by large-scale production methods while molded tablets generally involve small-scale operations. The various tablet types and abbreviations used in referring to them are listed below.

Compressed Tablets (CT)

These tablets are formed by compression and contain no special coating. They are made from powdered, crystalline or granular materials, alone or in combination with binders, disintegrants, lubricants, diluents and in many cases, colorants.

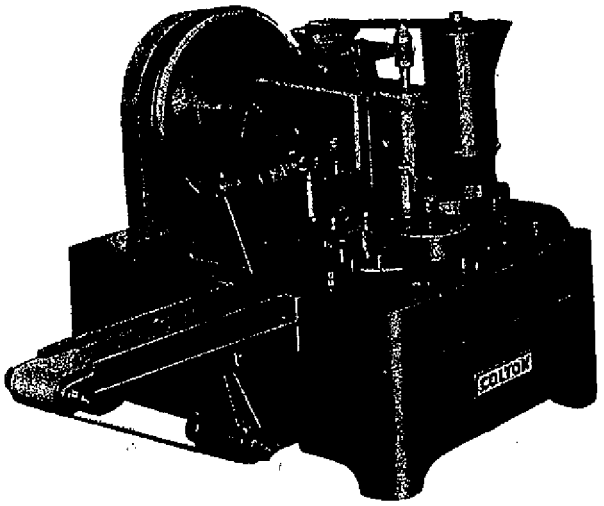

Fig 89-33. Automatic tablet triturate machine (courtesy, Vector-/Colton).

trated in Fig 89-33 makes tablet triturates at a rate of 2500/min. For machine-molding, the powder mass need not be as moist as for plate-molding since the time interval between forming the tablets and pressing them is considerably shorter. The moistened mass passes through the funnel of the hopper to the feed plates below. In this feed plate are four holes having the same diameter as the mouth of the funnel. The material fills one hole at a time and, when filled, revolves to a position just over the mold plate. When in position the weighted pressure foot lowers and imprisons the powder. At the same time a spreader in the sole of the pressure foot rubs it into the mold cavities and evens it off so that the triturates are smooth on the surface and are of uniform density. When this operation is completed, the mold passes to the next position, where it registers with a nest of punches or pegs which eject the tablets from the mold plate onto a conveyor belt. The conveyor belt is sometimes extended to a length of 8 or 10 ft under a battery of infrared drying lamps to hasten the setting of the tablets for more rapid handling. This method of drying can be used only if the drug is chemically stable to these drying conditions.

Compressed Tablet Triturates

Frequently, tablet triturates are prepared on compression tablet machines using flat-face punches. When solubility and a clear solution are required, water-soluble lubricants must be used to prevent sticking to the punches. The granulations are prepared as directed for ordinary compressed tablets; lactose generally is used as the diluent. Generally, tablet triturates prepared by this method are not as satisfactory as the molded type regarding their solubility and solution characteristics.

Capsules

Capsules are solid dosage forms in which the drug substance is enclosed in either a hard or soft, soluble container or shell of a suitable form of gelatin. The soft gelatin capsule was invented by Mothes, a French pharmacist in 1833. During the following year DuBlanc obtained a patent for his soft gelatin capsules. In 1848 Murdock patented the two-piece hard gelatin capsule. Although development work has been done on the preparation of capsules from methylcellulose and calcium alginate, gelatin, because of its unique properties, remains the primary composition material for the manufacture of capsules. The gelatin used in the manufacture of capsules is obtained from collagenous material by hydrolysis. There are two types of gelatin, Type A, derived mainly from pork skins by acid processing, and Type B, obtained from bones and animal skins by alkaline processing. Blends are used to obtain gelatin solutions with the viscosity and bloom strength characteristics desirable for capsule manufacture.[42]

The encapsulation of medicinal agents remains a popular method for administering drugs. Capsules are tasteless, easily administered and easily filled either extemporaneously or in large quantities commercially. In prescription practice the use of hard gelatin capsules permits a choice in prescribing a single drug or a combination of drugs at the exact dosage level considered best for the individual patient. This flexibility is an advantage over tablets. Some patients find it easier to swallow capsules than tablets, therefore preferring to take this form when possible. This preference has prompted pharmaceutical manufacturers to market the product in capsule form even though the product already has been produced in tablet form. While the industry prepares approximately 75% of its solid dosage forms as compressed tablets, 23% as hard gelatin capsules and 2% as soft elastic capsules, market surveys have indicated a consumer preference of 44.2% for soft elastic capsules, 39.6% for tablets and 19.4% for hard gelatin capsules.[43]

Hard Gelatin Capsules

The hard gelatin capsule, also referred to as the dry-fille capsule (DFC), consists of two sections, one slipping over th other, thus completely surrounding the drug formulation The classic capsule shape is illustrated in Fig 89-34. Thes capsules are filled by introducing the powdered materia into the longer end or body of the capsule and then slippin on the cap. Hard gelatin capsules are made largely fro gelatin, FD&C colorants and sometimes an opacifying age such as titanium dioxide; the USP permits the gelatin f this purpose to contain 0.15% sulfur dioxide to prevent d composition during manufacture. Hard gelatin capsul contain 12 to 16% water, but the water content can va depending on the storage conditions. When the humidity low, the capsules become brittle; if stored at high humiditi the capsules become flaccid and lose their shape. Storage high temperature areas also can affect the quality of ha gelatin capsules. Gelatin capsules do not protect hygr scopic materials from atmospheric water vapor as moistu can diffuse through the gelatin wall.

Companies having equipment for preparing empty ha gelatin capsules include *Lilly, Parke-Davis, Scherer* a *SmithKline*. The latter's production is mainly for its o use; the others are suppliers to the industry. With t

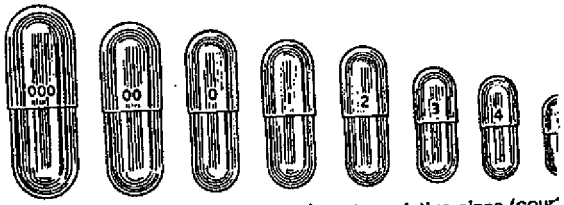

Fig 89-34. Hard gelatin capsules showing relative sizes (cour Parke-Davis).

the make and model, speeds from 9000 to 150,000 units per hour can be obtained (see Figs 89-41, 89-42 and 89-43).

All capsules, whether they have been filled by hand or by machine, will require cleaning. Small quantities of capsules may be wiped individually with cloth. Larger quantities are rotated or shaken with crystalline sodium chloride. The capsules then are rolled on a cloth-covered surface.

Uniformity of Dosage Units

The uniformity of dosage forms can be demonstrated by either of two methods, weight variation or content uniformity. Weight variation may be applied where the product is a liquid-filled soft elastic capsule or where the hard gelatin capsule contains 50 mg or more of a single active ingredient comprising 50% or more, by weight, of the dosage form. See the official compendia for details.

Disintegration tests usually are not required for capsules unless they have been treated to resist solution in gastric fluid (enteric-coated). In this case they must meet the requirements for disintegration of enteric-coated tablets. For certain capsule dosage forms a dissolution requirement is part of the monograph. Procedures used are similar to those employed in the case of compressed tablets. (See Chapter 31).

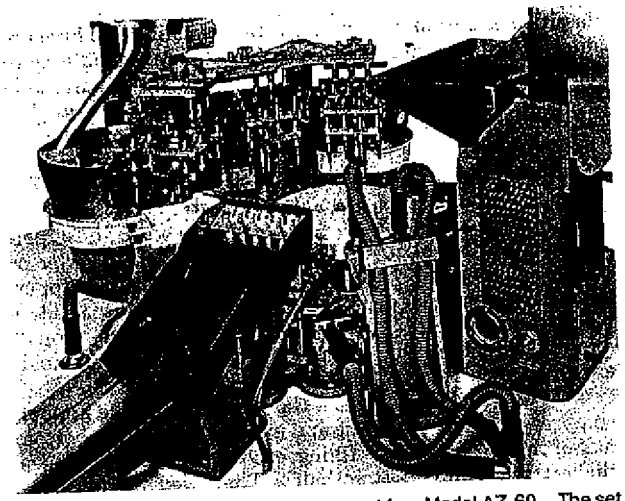

Fig 89-42. Zanasi automatic filling machine, Model AZ-60. The set of filling heads shown at the left collects the powder from the hopper, compresses it into a soft slug and inserts it into the bottom half of the capsule (courtesy, United Machinery).

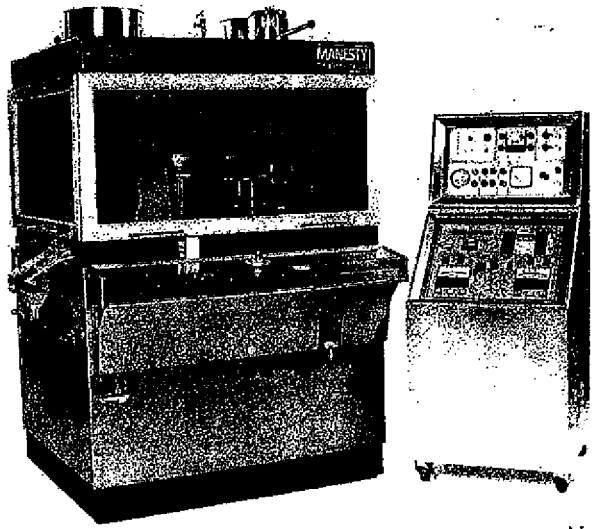

Fig 89-43. Hoefliger & Karg automatic capsule-filling machine, Model GFK 1200 (courtesy, Amaco).

Soft Elastic Capsules

The soft elastic capsule (SEC) is a soft, globular, gelatin shell somewhat thicker than that of hard gelatin capsules. The gelation is plasticized by the addition of glycerin, sorbitol or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of fungi. Commonly used preservatives are methyl- and propylparabens and sorbic acid. Where the suspending vehicle or solvent can be an oil, soft gelatin capsules provide a convenient and highly acceptable dosage form. Large-scale production methods generally are required for the preparation and filling of soft gelatin capsules. Formerly, empty soft gelatin capsules were available to the pharmacist for the extemporaneous compounding of solutions or suspensions in oils. Commercially filled soft gelatin capsules come in a wide choice of sizes and shapes; they may be round, oval, oblong, tube or suppository-shaped. Some sugar-coated tablets are quite similar in appearance to soft gelatin capsules. The essential differences are that the soft gelatin capsule has a seam at the point of closure of the two halves, and the contents can be liquid, paste or powder. The sugar-coated tablet will not have a seam but will have a compressed core.

Oral SEC dosage forms generally are made so that the heat seam of the gelatin shell opens to release its liquid medication into the stomach less than 5 min after ingestion. Its use is being studied for those drugs poorly soluble in water having bioavailability problems. When used as suppositories, it is the moisture present in the body cavity that causes the capsule to come apart at its heat-sealed seam and to release its contents.

Plate Process

In this method a set of molds is used. A warm sheet of prepared gelatin is laid over the lower plate and the liquid is poured on it. A second sheet of gelatin is carefully put in place and this is followed by the top plate of the mold. The set is placed under the press where pressure is applied to form the capsules which are washed off with a volatile solvent to remove any traces of oil from the exterior. This process has been adapted and is used for encapsulation by *Upjohn*. The sheets of gelatin may have the same color or different colors.

Rotary-Die Process

In 1933 the rotary-die process for elastic capsules was perfected by Robert P Scherer.[45] This process made it possible to improve the standards of accuracy and uniformity of elastic gelatin capsules and globules.

The rotary-die machine is a self-contained unit capable of continuously and automatically producing finished capsules from a supply of gelatin mass and filling material which may be any liquid, semiliquid or paste that will not dissolve gelatin. Two continuous gelatin ribbons, which the machine forms, are brought into convergence between a pair of revolving dies and an injection wedge. Accurate filling under pressure and sealing of the capsule wall occur as dual and coincident operations; each is delicately timed against the other. Sealing also severs the completed capsule from the net. The principle of operation is shown in Fig 89-44. See also Fig 89-45.

By this process the content of each capsule is measured individually by a single stroke of a pump so accurately constructed that plunger travel of 0.025 in will deliver 1 mg